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EXAMINER	
SALMON, KATHERINE D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,693	BERLIN ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 11/10/2009

2. Currently Claims 1-4, 6, 8-14 are pending. Claims 5, 7, 15-16 have been cancelled.

3. The following rejections for claims 1-4, 6, 8-14 is necessitated by amendment. It is noted that the rejections have been altered to encompass new limitations in the claims.

4. This action is FINAL.

Withdrawn Rejections

5. The 35 USC 112/2nd paragraph rejection and the 35 USC 112/Written Description made in section 4 and 6 of the previous office action is moot based upon amendments to the claims.

Claim Rejections - 35 USC § 112/Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6, 8-11, 13-14, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the art does enable one of skill in the art to analyze cytosine methylation in free floating DNA neither the art nor the specification enables one of skill in the art to determine the presence of a cancer based upon an increased amount of organ specific free floating DNA.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

The claims are drawn to a method of determining the fraction of total free floating DNA in a bodily fluid that originates from a specific organ comprising obtaining a bodily fluid, subjecting the free floating DNA to methylation and determining the amount or presence of free floating DNA that originates from a particular organ with that of a normal control value and detecting an cancer characterized by an increased amount of organ specific free floating DNA. The claims are further drawn to comparing the total amount of free floating DNA and the fraction of free floating DNA that originates form the organ and detecting an cancer characterized by an increased amount of organ specific free floating DNA. The claims are further drawn to determination of an

increased amount of free floating DNA that originates from an organ and detecting an cancer characterized by an increased amount of organ specific free floating DNA.

Therefore the claims are drawn to detection of the presence or an increase amount of free floating DNA originating from a particular organ and correlating the detection with the presence of any cancer characterized by an increased amount of organ-specific free floating DNA as compared to a normal control value.

Nature of the Invention

The claims are broadly drawn to a method of determining any DNA methylation pattern for any organ and detection of the presence of any cancer. The claims broadly encompass determining the presence of ANY cancer condition that originates from ANY organ by detection of the presence of any type of methylation pattern. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification asserts a means to predict which organ has developed a medical condition, by employing means of distinguishing between DNA originating from different healthy or different organs of the human body (p. 19 last paragraph). The specification asserts characteristic methylation patterns of certain genes can be

positively correlated with specific organs (p. 19 last paragraph).

The specification does not provide a predicative association of the detection of any cancer by the detection methylation patterns. The specification asserts the knowledge achieved allows predicting if the individual carries a medical condition, such as a cell proliferative cancer in said organ (p. 22 5th paragraph). The specification asserts a patient with a substantial amount of free floating DNA originating from liver, might have developed a liver tumor (p. 22 5th paragraph). The specification asserts that to validate this, the next step could be to employ, for example, a tailored test assay for cancer indicating marker gene expression, specific for said organ or tissue (p. 22 5th paragraph). Therefore the specification asserts that validation studies are sometimes needed to clearly associate detection of free floating DNA with detection cancer.

The specification asserts that methylation patterns found in the tested sample will be identified as belonging to a certain organ (p. 34 5th paragraph). The specification asserts that methylation patterns can be associated either by comparing the individual data set resulting from said analysis to data received in previous studies or to a dataset obtained in a parallel experiment on one or preferably more control fluids (p. 34 last paragraph). The specification indicates that to determine if methylation patterns are associated with cancer a comparison study must be done, however, the claims as broadly written merely comprise the detection of methylation patterns.

Post filing art, Cottrell (clinical Biochemistry 2004 Vol. 37 p. 595) teaches that because methylation-based markers are not routinely used in clinical labs, the methodology has not been fully optimized, validated, and standardized. Cottrell et al.

teaches that most of the methylation methods rely on bisulfite treatment protocol which must meet strict requirements for consistency and performance (p. 601 1st column 2nd full paragraph). Cottrell et al. teaches that in order to discover optimal markers and create successful assays, there will need to be clearly defined clinical questions, sample sets, and methodologies coupled with the current methylation technologies (p. 601 1st column last paragraph). Based on the data presented in the specification and the teachings in the art, it is unpredictable to correlate the methylation pattern of any free floating DNA to ANY cancer condition by detecting methylation patterns. The art teaches the lack of predictability with regard to methylation pattern studies and correlation to any cancer condition.

Figure 7 is disclosed in the specification as the result of the study wherein DNA methylation pattern of specific CpGs in DNA from four different tissues has been analyzed (p. 42). The specification discloses that methylation analysis from CpG positions correlate to the specific tissue types (p. 43). However, the art as exemplified by Cottrell et al. teaches that using circulating DNA as a diagnostic tool is unpredictable and that methylation patterns are not reproducible. Therefore the specification, even though it shows that one can detect methylation positions, does not provide guidance as how to use such methodology to detect the presence of a cancer derived from the organ.

In summary, the claims encompass the detection of any cancer using samples from by the detection of free floating DNA or the detection of methylation patterns of free floating DNA, however, the specification does not provide guidance as to how to make

associations between any cancers in an individual by the detection of free floating DNA. Moreover, the specification indicates that the correlation of cancer and free floating DNA must have an association step to compare to a validation study. The associations are unpredictable, because the specification provides no statistically significant association between any cancer and detection of free floating DNA, further the art teaches that theses associations are unpredictable.

Working Examples

The specification provides no examples to correlate detection of a specific cancer by detection of free floating DNA in any individual. Example 1 describes determining plasma blood from one patient to detect neoplastic cancer (p. 43). The specification asserts that it was concluded a significant portion of the DNA in the patient's blood derived from his lung, the physician now referred the patient to a hospital that is specialized on inflammatory or cell proliferative cancers of the lung. However, the specification does not provide any pvalue, therefore, it is unclear how to extrapolate the example of one specific patient to the detection of a large portion of DNA derived from lung to the detection of any cancer by detection of free floating DNA.

The specification asserts three more patient samples with detection of serum DNA levels (p 43-44), however there are no working examples showing a statistically significant association of any cancer. The first three experiments only had an association of a specific patient and a specific cancer, whereas it is unclear the number of patients in the 4^{th} experiment.

Furthermore, the specification provides no indication as to whether the detection of a methylation pattern is significant such that the skilled artisan would be able to predictably correlate the results which any cancer condition. The specification does not

have an example of determining in any sample a correlation of methylation pattern with detection or ANY cancer condition.

Therefore, though the specification provides a few studies of the correlation of one patient and the detection of one tissue type and as presented in figure 7 the correlation of specific CpG island methylation patterns and organ type, the art as discussed above teach that these associations are unpredictable. Further, the guidance in the specification only indicates that an increased level of organ specific free floating DNA is indicative of an organ based cancer, but not a specific cancer. Further, it is well known that some cancer have effects on multiple organs. For example, Paredes-Zaglul et al. (Clinical Cancer Research Vol. 4 April 1998 p. 879) teaches that colon cancer spreads to the liver (p. 879 2nd column 1st paragraph). Therefore it would be unclear if an elevated free floating DNA amount in the liver would be indicative of a liver based cancer or rather a colon based cancer. The art teaches that the correlation of methylation patterns to any cancer in any given population is not reproducible. The skilled artisan, therefore, would have to perform undue experimentation in order to determine if methylation patterns in circulating DNA is correlative to any cancer.

The predictability or unpredictability of the art and degree of experimentation

The art teaches that there is unpredictability in associating circulating DNA (free floating) with cancer. The post-filing art, Bremnes et al. (Lung Cancer 2005 Vol 49 p. 1) teaches a review of circulating DNA in lung cancer by evaluating the role of circulating DNA in 22 studies (abstract). Bremnes et al. teaches the analysis of circulating DNA in plasma might lead to increasing clinical impact, however, large perspective clinical studies are needed to validate and standardize any test for DNA alteration in plasma or

serum of high risk individuals or patients with established lung cancer (Abstract). Therefore there is still unpredictability with correlating circulating DNA in plasma and serum with cancer condition. The combined data from those studies indicated that circulating DNA levels were increased in about 61% of the cancer cases. Similarly, the methylation levels of different genes varied from 5 to 73%, depending on the gene (Table 4; page 8, third paragraph). In conclusion, the authors state (Abstract):

"The analysis of circulating DNA or RNA in plasma is a promising non-invasive diagnostic tool, requiring only a limited blood sample. Its wide applicability and potential importance will possibly lead to increasing clinical impact in the near future. However, large prospective clinical studies are needed to validate and standardize any tests for DNA or RNA alteration in plasma or serum of high risk individuals or patients with established lung cancer."

Therefore, circulating DNA and its relationship to cancer diagnosis remains an interesting clinical research topic, but not a diagnostic tool.

Jung et al. (Cancer Letters 2004 Vol 205 p. 173) teaches the presence of circulating DNA (free floating) in patients with prostate cancer and benign prostate hyperplasia (BPH) (abstract, page 174-175 1st two paragraphs). Juang et al. teaches that patients with metastases had higher levels of circulating DNA, the DNA levels in cancer patients without metastases were not significantly different from the normal controls, whereas some of the BPH patients had circulating DNA levels higher than normal (p. 175-176 and Figure 2). Therefore Jung et al. indicates that that circulating DNA levels vary according to the cancer, whereas cancer patients had different levels of

circulating DNA compared to patients with metastases. Therefore it is unpredictable that comparison of circulating DNA to a control would indicate a particular cancer.

As evidenced by current literature, circulating DNA is not always correlated with the presence of cancer in a subject. Sidransky et al. (Ann. NY Acad. Sci.,2000 vol. 906, pp. 1), the origin of circulating DNA in the blood is uncertain (page 3, second paragraph), and "these studies raise significant issues about the biology and physiology of how the DNA is released and maintained in the circulation and ultimately on its clinical value" (page 3, third paragraph). Sindransky states further "However, it is abundantly clear that large prospective studies with longitudinal follow up are essential if we are to carefully evaluate these circulating DNA markers and eventually integrate them into the clinical setting." Therefore elevated DNA levels are not indicative that the patient has any particular organ based cancer, but rather an indication that other validation studies must be performed.

The current art teaches that methylation is not only caused by neoplasms, but that methylation can be detected in normal tissue. This indicates that detection of methylation does not indicate neoplastic tissue. The current art teaches detection of methylation is indicative of not only neoplasm but also aging of normal cells. Yates et al. (Oncogene 2006 Vol 25 p. 1984) teaches that methylation increases with age and malignancy (abstract). Yates et al. teaches that methylation was detected in urine DNA from patients with and without bladder cancer (Abstract). Yates et al. teaches aberrant methylation is not cancer specific and can be found in a normal ageing cell population (p. 1985 1st column 1st paragraph). Yates et al. teaches the overall knowledge of the

molecular mechanisms of DNA methylation in health and cancer remains poor and one uncertainty is the extent of aberrant DNA methylation in nonmalignant tissue and the association between ageing and aberrant DNA methylation (p. 1985 last paragraph). Therefore in a given patient elevated free floating DNA from a particular organ compared to a normal control might be indicative of the aging of the patient rather than a particular cancer.

Lui et al. (Clin Chem Lab Med 2002 Vol. 40 p. 962-968) teaches that circulating DNA is present in increased amounts in transplant patients (p. 963 last two paragraph and p. 964 1st paragraph) and in trauma patients (p. 964 2nd paragraph). Therefore the presence of cancer is not the only source of circulating DNA in the body. Further, medical transplantation and physical trauma can effect an individual's free floating DNA level, therefore it is unclear if an elevation compared to a normal control is indicative of a particular cancer, or rather a physical trauma which has occurred on the patient's body.

The art presented shows the unpredictability of determining the methylation profiles of organs and tissues for comparison to detect cellular proliferation. Eckhardt et al. (Nature Genetics 2006 Vol. 38 p. 1378) teaches methylation patterns for three human chromosomes from a representative number of healthy human tissues and primary cells (p. 1378 2nd column 1st paragraph). Eckhardt et al. teaches methylation patterns are influenced by a number of endogenous and exogenous parameters (p. 1381 1st column last paragraph). Eckhardt et al. teaches that tissue (e.g. organ) samples may be inherently more heterogeneous than primary cells because of the

different cell types constituting a given tissue (p. 1382 1st column 2nd paragraph). Eckhardt et al. teaches that some tissue such as lung and colon will show a stronger correlation between age and methylation (p. 1382 1st column 2nd paragraph). Therefore the postfiling art teaches determining a methylation pattern that is characteristic for a particular tissue, cell type or organ to detect the presence of a cellular proliferative cancer is unpredictable. Eckhardt et al. teaches that different profiles can be obtained depending on the age. Eckhardt et al. teaches that the profile of some tissues contains heterogeneousity because of the varying cell types in the tissue. Eckhardt et al. teaches that tissue samples may be inherently more heterogeneous than primary cells because of the different cell types constituting a given tissue (p. 1382 1st column 2nd paragraph). Eckhardt et al. teaches that some tissue such as lung and colon will show a stronger correlation between age and methylation (p. 1382 1st column 2nd paragraph).

Raykan et al. et al. (PLOS Biology December 2004 Vol. 2 p. e405) teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (e.g. organs) (p. 2171 2nd column last paragraph). Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and cancer state (p. 2176 last paragraph). Therefore Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a particular tissue, cell type, or organ without determining the differences in the

methylation patterns between individuals. In other words, it would be unpredictable that the level of free floating DNA detected was from a particular tissue type or from differences between individuals.

Therefore the comparison of a sample in one patient to a profile might indicate that there is a high level of certain methylation sites, however, this methylation pattern could be due to developmental stage, age, and cancer state of the patient.

Dennis et al. (US Patent Application Publication 2003/0044388 March 6, 2003 filed August 31, 2001). Dennis et al. teaches obtaining a bodily fluid from a human sample (e.g. plasma or serum) (p. 2 paragraph 9). Dennis et al. teaches detecting the amount of DNA (e.g. in plasma and therefore free floating) that originates from a particular organ comprising analyzing a DNA methylation pattern p. 2 paragraph 9). Dennis et al. teaches determination of a cancer characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the cancer is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches comparisons of the methylation status with control subjects (paragraph 43 p. 5). It appears that the teachings in Dennis et al. and the instant specification are commensurate, however, the specification does not appear to add anything further to the teachings of the prior art. Based upon the evidence presented in the instant specification it is not clear that the instant specification provides enabling support, however, if the specification is found to be enabling, in order to have compact prosecution a 35 USC 102 rejection has been made over Dennis et al. and is presented below.

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate detection of any cancer by the detection of free floating DNA. The specification discloses that a correlation to cancer must include an association step to compare methylation patterns to individuals and a validation study to confirm detection of cancer.

The art teaches detection of cancer with methylation patterns in free floating DNA is unpredictable and that these associations need to be confirmed by multiple large sampling sizes to determine a clear association. The skilled artisan, therefore, would have to perform undue experimentation to determine the correlation of cancer detection to detection of free floating DNA as it is broadly written in the claims.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written. The skilled artisan would have to determine the association of any detection of cancer with measurement of free floating DNA. The skilled artisan would then have to determine if this association was species base. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide any predictable association of detection of free floating DNA and any cancer. Further the art teaches that the measurement of free floating DNA and associations made are unpredictable. In view of this unpredictability, the specification has not established that the presently claimed method can be used to determine the detection of any cancer by the detection of free floating DNA or methylation patterns of free floating DNA.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Arguments

The reply traverses the rejection. A summary of the reply is presented below with response to arguments following. The reply summarizes the 35 USC 112 rejection presented in the previous office action (p. 16-18). The reply provides relevant law (p. 19-20).

(A)The reply asserts that there has not been a prima facie case of lack of enablement because the degree of experimentation is not undue experimentation but rather routine experimentation (p. 20 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Though the skilled artisan would be able to perform a method of determining the amount of free floating organ DNA in a sample, it would be unpredictable to use such a method to predict a cancer as exemplified by the claims. As shown above, the specification does not provide a specific example of detection of any specific cancer, whereas the art teaches that such correlations are unpredictable. For example, as discussed above Raykan et al. et al. (PLOS Biology December 2004 Vol. 2 p. e405) teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (e.g. organs) (p. 2171 2nd column last paragraph). Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and cancer state (p. 2176 last paragraph). Therefore Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a

particular tissue, cell type, or organ without determining the differences in the methylation patterns between individuals. Such experimentation is not routine, but rather, requires the skilled artisan to perform many experiments on different samples with many intervening steps without a guarantee of success. Therefore as discussed above, the experimentation required would be considered unpredictable based upon the lack of guidance in the specification and the unpredictable with such associations as exemplified by the cited art.

(B) The reply asserts that it is improper to construe a validation study must be necessary to associate detection of free floating DNA with detection disease (p. 22 1st paragraph). The reply asserts that the applicants have taught a correlation can be made between a substantial mount of free floating DNA originating from the liver and that fact that the patient bears a diseased liver (p. 22 1st paragraph). The reply asserts that the applicants have previously amended the claims to include a comparison with a normal control value.

These arguments have been fully reviewed but have not been found persuasive.

It is the examiners position that although one could detect an increased amount of free floating DNA originating form a particular organ, that this increased amount is not directly correlative to the presence of a cancer, but rather, the art as cited above has indicated that increased free floating DNA from a particular organ could be due to many other disease related problems. For example, Lui et al. teaches that an elevation can be due to a physical trauma on the patient's body. Although the applicant has amended

the claims to a control normal value, the instant specification has not provided limitations as to how much increase of free floating DNA is correlative to cancer. For example, Raykan et al. teaches that methylation levels vary by more than 20% between individuals and tissues. Therefore depending on the normal control and the individual there are differences in levels of methylation which would be due to the individual variability and not due to cancer. The instant specification has not provided any support as to which levels of increase are correlative, nor has the instant specification provided any p values showing such correlation to cancer.

(C) The reply asserts that although the applicants recognized through the teaching of Cottrell that methylation studies must be adequately tested, the art at the time of filing allowed for a quick and efficient method of simultaneously testing thousands of CpG sequences (p. 22 last paragraph-p. 23 1st paragraph). The reply asserts that the claims are limited to detection of cancer of particular organs that are accompanied by an increased level of a particular organ specific DNA in the blood or body fluid (p. 23 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Although it is acknowledged that high throughput analysis allows for the detection of CpG sequences, this analysis does not provide the predictable association of increased levels of organ specific DNA to cancer. For example, Lui et al. teaches that these increased levels can be due to bodily trauma. Therefore just because there is a higher level of organ specific DNA in the body fluid does not mean that the patient has

cancer, rather, it could indicate many problems in the body including age, cell death, and trauma.

(D) The reply asserts that the source of the whole amount of free floating DNA in the blood may be caused by a variety of reasons as evidenced by Jahr et al and Anker et al. (p. 23 2nd paragraph). The reply asserts that it is irrelevant because it is the amount of organ specific circulating DNA which is correlated to the presence of a diseased organ.

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be indicating that a specific amount of circulating DNA is directly correlative to cancer. However, the instant specification has not provided any guidance as to which increased level is correlative to cancer. Further, the claims are drawn to increased levels based upon a comparison of a normal control value. As taught by Raykon et al. an individual might have at least a 20% difference compared to a normal. Herein in this case it is not clear at what level does the amount of organ specific DNA correlate to cancer and not to other traumas to the body.

(E) The reply asserts that "elevated levels of circulating DNA appear to be characteristic for most but not all of the carcinoma diseases" (p. 23 last full paragraph). The reply points to Figure 3 as showing results of determining increased free floating levels.

These arguments have been fully reviewed but have not been found persuasive.

However, as indicated above, the claims are drawn to detecting cancer based upon increased levels. Although these increased levels might indicate cancer, increased levels are also associated with a number of other conditions of the body. Further, Figure 3 discloses that free floating DNA can be detected in serum. Although the levels of this free floating DNA is higher in patients with lung cancer, colon, and breast cancer as compared to healthy (p. 41 of the specification), the claims are drawn to detecting cancer based upon elevated levels of organ specific DNA. Herein in the instant case, higher levels of free floating DNA is also due to age, trauma, and individual differences in methylation. Therefore higher levels of organ specific free floating DNA is not only due to cancer, but also due to many other bodily functions. As such detection of elevated levels is not directly correlative to detection of cancer.

(F) The reply assert that while the clinical value of the total amount of circulating DNA may be questionable or unpredictable, the analysis of organ specific fractions therein is highly informative (p. 24 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

However, the claims are drawn to detecting cancer based upon elevated levels of organ specific fraction. As discussed by the art cited above, such a correlation is unpredictable. Although the analysis of organ specific fractions might be informative, the analysis does not predictably detect cancer as is claimed.

(G) The reply asserts that that methylation patterns many not only be indicative

of cancer but also bear additional information such as aging and development (p. 24 1st full paragraph). The reply asserts that the claimed method uses the methylation status of CpG dinucleotides sequences as diagnostic tools where they are methylated in a pattern specific to a particular organ regardless of the age status (p. 24 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

However, the claims are drawn to detecting an increased level of organ specific free floating DNA compared to a normal control. The specification does not provide guidance as to how to determine rather an increased level is due to cancer or due to "additional information". Further, the specification does not describe the normal control. As such it is unclear how much difference in methylation patterns the patient must have compared to this control to have cancer. As acknowledged increased levels are due to other occurrences in the body besides cancer, however, the specification has not provided guidance as to when these occurrences are due to cancer versus age, trauma, ect.

(I) The reply asserts that with respect to age, transplant, and trauma that these increases in the subject would be reflected in the normal controls (p. 25 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The instant specification has not defined normal controls. Patterns of free floating DNA differ in each patient individually, as the patient ages and due to transplant and trauma. The reply seems to be asserting that all of these patterns would be evaluated by the normal control. However, it would be unpredictably what would be

considered a normal control for each individual. For example, the control could be normalized for the age of the patient, but it is unclear how to take every type of increased level of organ specific DNA into account it this control. As such the comparison step is not the only step necessary to determine the association of increased levels of DNA to other occurrences in the body that are not due to cancer.

(j) The reply asserts that that specification teaches than an increased level of organ specific circulating DNA is indicative of said disease organ.

These arguments have been fully reviewed but have not been found persuasive.

However, the claims are drawn to detection of cancer. Therefore the specification has not provided that increased levels of organ specific circulating DNA predictably detects cancer. The art has shown that increased levels can be due to other factors besides cancer.

(K) The reply asserts that the specification does not indicate that a correlation must include a validation study to confirm the detection of disease (p. 25 last full paragraph). The reply assert that rather the specification teaches that it is an option to further analyze the organ for further analysis by applying a cancer stage specific marker (p. 25 last full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

However, the instant specification has provided no examples wherein the increased level of organ specific DNA is associated with cancer in a patient. Figure 3

discloses that cancer samples have increased levels, however, the art teaches that detection of increased levels is observed for many reasons. As such although the specification does not indicate a validation study must be done, the specification has not provided a predictable association between increased levels and detection of cancer.

(L) The reply points to figures 4-7 and Examples 1-4 to show that the specification teaches that elevated levels of circulating DNA appear to be characteristic for most but not all of carcinoma diseases (p. 26 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

As discussed above Examples 1-4 and Figures 4-7 show that organ specific methylation patterns can be detected, however, in none of these examples and figures are elevated organ specific patterns directly correlated to cancer. For example in example 1 and individual was tested and it resulted in a higher amount of DNA from the lung being detected (p. 43). The specification asserts that the result was send back to the physician who referred the patient to a hospital that specialized in inflammatory or cell proliferative diseases. Therefore the elevated levels could not only be due to cell proliferative diseases but also to inflammatory diseases. As shown by the instant specification, therefore, elevated levels are not directly associated with cancer without further tests.

(M) The reply asserts that with respect to determination of cancer, that the association of free floating DNA to cancer is not undue but rather routine

experimentation (p. 27 1st paragraph). The reply asserts that the examiner has offered insufficient evidence to support that the experimentation is other than routine (p. 27 2nd paragraph). The reply asserts that the claims are limited to determination of human cancer characterized by increased amount of organ specific free floating DNA based on a normal control comparison (p. 27 last paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Although the assay to detect free floating DNA is not undue the association of this DNA level to detection of cancer requires experimentation which is unpredictable. Herein in the instant case, the art clearly shows that elevated levels of DNA can be dues to many factors. Further, even the instant specification teaches that further tests must be done to determine if the elevated levels are due to cancer or some other organ based disease (such as inflammatory disease) (see example 1 in specification).

(N) The reply asserts that claim 12 is allowable as it does not recited determination of cancer (p. 28 2nd full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that claim 12 is not rejected under 35 USC 112/Enablement, however, it has been rejected over the art as cited below.

(O) The reply asserts that detection of cancer with methylation patterns in free floating DNA is not unpredictable, as postfiling art has confirmed the use of colon cancer marker Septin 9 for methylation (p. 28 2nd full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

However, the claims are drawn to detection of any increased organ free floating DNA and associating it with any cancer. Although a specific marker might have been found after filing, this association to colon cancer required further experimentation on the part of the skilled artisan wherein the result (an association to cancer) was not predictably guaranteed. Herein in the instant case, the art at the time of filing indicated that increased levels could be due to many body issues. Further the specification taught that even if increased organ DNA levels were found that a further test to evaluate was used (e.g. to determine if the increased levels were due to cancer or inflammation). As such the detection of increased levels of organ specific DNA is not directly correlative to cancer.

(P) The reply asserts that there is no reason that 20% or greater variation at a given CpG would effect the utility of the claimed assay as this variation would be reflected in the normal control values and it would be overshadowed by increased levels of free floating DNA which can be hundreds of fold (p. 28 3rd full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

However, the specification has not described the term normal control in such a way that this difference between individual would be encompassed by the term normal control. Specifically, the specification has not provided which increased levels are associated with cancer. Therefore the claims are drawn to any level of increase being predicative of cancer. Herein in the instant case a 20% variation as taught by Raykan

would be higher than the normal control and as such would be encompassed by the claims.

(!) The reply asserts that the methylation pattern of the metastasized cells would retain the colon pattern even if colon cancer had moved to the liver (p. 28).

These arguments have been fully reviewed but have not been found persuasive.

This argument is unpersuasive, because it is not clear if the skilled artisan detects increased levels of liver free floating DNA if this would be directly correlative to colon cancer. Specifically, the skilled artisan would have to perform further tests on the patient to determine if the elevated levels are due to liver cancer, colon cancer, or another disease of the liver such as cirrhosis. As such the detection of elevated levels would not predictably detect cancer of a particular organ, as further tests must dot ermine such associations. Further the increased level of a particular organ DNA does not predictably guarantee the detection of a cancer, as the increased levels could be due to other diseases (such as cirrhosis).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. It is noted that the 35 USC 103(a) rejection presented below is based upon the obviousness of performing methylation specific analysis on an array and therefore does not contradict the unpredictability discussed in the 35 USC 112/enablement rejection disclosed above.

9. Claims 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dennis et al. (US Patent Application Publication 2003/0044388 March 6, 2003 filed August 31, 2001) in view of in view of Heiskanen et al. (Cancer Research 2000 Vol 60 p. 799).

With regard to Claim 12, Dennis et al. teaches obtaining a bodily fluid from a human sample (e.g. plasma or serum) (p. 2 paragraph 9). Dennis et al. teaches step of quantifying the total concentration of DNA in the biological sample can be performed (p. 2 paragraph 9 and p. 5 paragraph 43). Dennis et al. teaches detecting the amount of DNA (e.g. in plasma and therefore free floating) that originates from a particular organ comprising analyzing a DNA methylation pattern p. 2 paragraph 9). Dennis et al. teaches a method of methylation specific PCR wherein the DNA is subjected to chemical treatment to convert all unmethylated cytosines in the DNA into uracil but leaves position 5-methylatied cytosines unmodified (p. 3 paragraph 20). Dennis et al. teaches determination of a cancer characterized by increased amount of the concentration of DNA (p. 2 paragraph 9 and p. 5 paragraph 43). Such that the cancer is the presence of a gene associated with organ transplantation and the increased amount is the indication of a transplanted organ. Dennis et al. teaches that a further step of quantifying the total concentration of DNA in the biological sample (total free floating DNA) can be performed (p. 2 paragraph 9 and p. 5 paragraph 43).

With regard to Claim 14, Dennis et al. teaches using amplification procedures such as methylation specific PCR (p. 3 paragraph 20).

However Dennis et al. does not teach performing the method steps with the total DNA bound to the surface.

Heiskanen et al. teaches a method of taking a target DNA and binding it to a surface (microarray) before using the target to detect expression levels (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at

the time the invention was made to improve the method of Dennis et al. by binding the target DNA (free floating DNA) to a microarray as taught by Heiskanen et al. The ordinary artisan would be motivated to improve the method of Dennis et al. by binding the target DNA (free floating DNA) to a microarray as taught by Heiskanen et al. because Heiskanen et al. teaches that by binding the DNA to a microarray parallel analysis of genomic DNA for expression analysis allows for a rapid approach to the identification of amplified genes in tumor cells. Therefore it would be obvious to rapidly identify any changes in the genes including methylation changes by using microarray parallel analysis because this method allows for the detection of many changes in the sample (e.g. methylation) to be detected simultaneously.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply are summarized below with response to arguments following.

The reply asserts that the markers are not organ specific , but rather donor species (p. 30 1st full paragraph). The reply asserts that the art does not anticipate the claimed invention which recites the use of organ specific DNA methylation pattern and that the methylation pattern of Dennis et al would not distinguish between a given donor's own organs.

These arguments have been fully reviewed but are not found persuasive.

The claims are drawn to determining the amount of DNA in a bodily fluid that

originates from a specific organ and not distinguishing between organs. Herein in the instant case, the method of Dennis et al. would detect free floating DNA that originates from a specific organ (e.g. the donor organ) and as such anticipates all the claimed method steps.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

/Sarae Bausch/
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